REMARKS

Claims 1-43 are pending in the above-identified application. Claims 11-13 and 25-43 are withdrawn from consideration as being directed to a non-elected invention. Applicant reserves the right to prosecute these claims in a related application claiming priority to the above-identified application. Accordingly, claims 1-10 and 14-24 are currently under examination. Applicant has review the rejections set forth in the Office Action mailed January 28, 2004, and respectfully traverse all grounds for the reasons that follow.

With regard to the restriction of newly added claims 41-43, allegedly being directed to a non-elected invention, Applicant respectfully traverses this restriction. The newly added claims are encompassed within the claims currently under examination. For example, claims 41 and 42 depend from current claim 1 and include all the elements of that claim. The initial search with respect to the claims currently under examination encompasses at least claims 41 and 42. Therefore, these claims should be examined together with claims 1-10 and 14-24. Reconsideration and withdrawal of the restriction of new claims 41-43 is respectfully requested.

Rejections Under 35 U.S.C. § 112

Claims 1-10 and 14-24 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office asserts that it is unclear how each cell in the claimed cell composition can be made to express only a single variant nucleic acid with the exclusion of other variant nucleic acids and how the variant nucleic acid is located within each of the different cells at an identical site in the genome.

Applicant contends that the claims are clear and definite as written. The invention claims a cell composition comprising a population of non-yeast eukaryotic cells, wherein each cell expresses a single variant nucleic acid of a population of variant nucleic acids. The application teaches, for example, at page 16, lines 14-23, that single variant nucleic acids

can be inserted at an identical site in the genome of cells within a population to create isogenic cell lines, differing only in the expression of a particular variant or heterologous nucleic acid. Methods for inserting variant nucleic acids at a single site in the genome are described, for example, beginning at page 16, line 24. Accordingly, the invention claims a population of non-yeast eukaryotic cells. The express language of the claims recite that each cell within the population of non-yeast eukaryotic cells express a single variant nucleic acid of a population of variant nucleic acids. Further, the application teaches the generation of isogenic cell lines expressing different variant nucleic acids at an identical site in the genome. Therefore, the claims are sufficiently clear and definite to satisfy the requirements of the second paragraph of § 112 and withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 1, 10, 14 and 24 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Stemmer, U.S. Patent No. 6,132,970. The Office points to several passages in Stemmer, allegedly describing a cell composition transfected with a vector containing variants of a nucleic acid, and asserts that the transfected cells correspond to the claimed non-yeast eukaryotic cells.

Applicant submits that Stemmer does not describe all elements of the claimed invention. For example, Stemmer fails to describe a population of non-yeast eukaryotic cells. Further, Stemmer also fails to describe a non-yeast eukaryotic cell composition having a diverse population of about 10 or more variant nucleic acids wherein each variant nucleic acid is located within each cell at an identical site in the genome. In this regard, Stemmer is directed to methods of shuffling polynucleotices. The passages cited by the Office appear to describe the construction of a CDR library and transfection via electroporation into host cells (col. 52, line 66 through col. 53, line 7). Stemmer transfects either TG-1 or JC8679 *E. coli* cells which are not eukaryotic cells (col. 52, lines 66-67). Further, the transfection of bacterial cells using the plasmids described by Stemmer do not incorporate into the bacterial genome nor do they incorporate at an identical site in the

genome. Therefore, the claimed invention is distinct from Stemmer and withdrawal of this ground of rejection is respectfully requested.

Claims 1-6, 8, 10, 14-17, 20 and 22-24 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Choi et al., Nucleic Acids Res. 28:e19 i-vii (2000). The Office alleges that Choi et al. describe a plant cell transfected with a vector containing a BAC library. Figure 1 and pages iii and vii of Choi et al. are pointed to as support that this description corresponds to the claimed non-yeast eukaryotic cells.

Applicant submits that Choi et al. do not describe all elements of the claimed invention. For example, Choi et al. fail to describe a non-yeast eukaryotic cell composition having a diverse population of about 10 or more variant nucleic acids wherein each variant nucleic acid is located within each cell at an identical site in the genome. The BAC vectors and libraries are distinct from variant nucleic acids located within each cell of a population at an identical site in the genome. In this regard, a BAC vector is a vector, not a genome. Figure 1 of Choi et al. appears to describe insertion of DNA fragments into pBACwich, which is a BAC vector and not a genome. Similarly, the descriptions on pages iii and vii also describe the use of BAC vectors. Therefore, Choi et al. fail to describe the insertion of variant nucleic acids located within cells of a population at an identical site in the genome of non-yeast eukaryotic cells. Accordingly, the claimed invention is distinct from Choi et al. and withdrawal of this ground of rejection is respectfully requested.

Claims 1-10 and 14-24 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Zarling et al., US 2003/0105039. The Office alleges that Zarling et al. describe at paragraphs 127-129 a composition including insect , *xenopus*, rodent, primate or human cells transfected with vectors containing pools or libraries of variant nucleic acid sequences that correspond to the claimed non-yeast eukaryotic cells.

Applicant submits that Zarling et al. do not describe all elements of the claimed invention. For example, Zarling et al. fail to describe a cell composition transfected with a diverse population of about 10 or more variant nucleic acids wherein each transfected variant nucleic acid is located within each cell at an identical site in the genome. In this regard, Zarling et al. appears to describe mutagenesis of an endogenous sequence.

Paragraphs 127-129 of Zarling et al. describe that the methods are "similar to traditional site-directed mutagenesis and PCR mutagenesis." Further, Zarling et al. describe the use of pairs of targeting polynucleotides that "due to the random nature of the paring, one or both of any particular pair of single-stranded targeting polynucleotides may not contain any mismatches" (paragraph 129). Therefore, Zarling et al. describe the mutagenesis of an endogenous sequence, which is distinct from the claimed cell composition containing non-yeast eukaryotic cells transfected with a diverse population of 10 or more variant nucleic acids. Withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S. C. § 103

Claims 1-10 and 14-24 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Stemmer, *supra*, in view of Biard-Piechczyk et al., *Human Antibodies* 9:67-77 (1999). The Office acknowledges that Stemmer does not describe recombination using loxP-Cre but alleges that Biard-Piechczyk et al. describe that loxP-Cre results in selection of nucleic acid variants encoding antibodies with higher affinities.

To establish a *prima facie* case of obviousness, the Office must show that the prior art would have suggested the claimed invention to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000). The first prong of this test is unsatisfied because the Office simply asserts that the method Biard-Piechczyk et al. can be used for its advantageous effect of obtaining a product from the library with higher affinities. However, there has been no showing that such a general conclusion is supported by the cited art, particularly in light of the language cited by the Office.

In this regard, Biard-Piechczyk et al. state "[h]ere we report for the first time the obtention of human scFvs from a combinatorial library using the loxP-Cre system to link VH and VL genes." Page 72, paragraph 1. In contrast to the assertions in the Office Action, Biard-Piechczyk et al. do not describe that the use of loxP-Cre results in selection of antibodies with higher affinities. Instead, Biard-Piechczyk et al. describe that a panning procedure may lead to selection of higher affinity antibodies. Therefore, any implication regarding an alleged advantage for selecting higher affinity antibodies is linked to the

panning method and not to the loxP-Cre system. Accordingly, Biard-Piechczyk et al. fail to describe a desirability for combining the loxP-Cre system with Stemmer. Further, both Stemmer and Biard-Piechczyk et al. utilize bacterial cells. There is no teaching or suggestion within these references to use non-yeast eukaryotic cells. Therefore, the cited references fail to suggest the invention as claimed.

Establishing that the cited art would have suggested the claimed invention requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an "essential evidentiary component of an obviousness holding." *Brown & Williamson Tobacco*, 229 F.3d at 1124-25 (*quoting C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1351-52 (Fed.Cir.1998); *see also C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art where to select the components that the inventor selected and use them to make the new device); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) (there must be some motivation, suggestion or teaching in the prior art of the desirability of making the specific combination that was made by the applicant). The evidentiary showing must be clear and particular and broad conclusory statements about the teachings of the cited references, standing alone, are not "evidence." *Brown & Williamson Tobacco*, 229 F.3d at 1125 (*quoting In re Dembiczak*, 175 F.3d 994, 1000 (Fed.Cir.1999), abrogated on other grounds by *In re Gartside*, 203 F.3d 1305, 53 USPQ2d 1769 (Fed.Cir.2000)).

In the pending Office Action, there has been no underlying factual showing that it would have been obvious to one of ordinary skill in the art to have modified the cells of Stemmer with the loxP-Cre system of Biard-Piechczyk et al. to obtain the claimed non-yeast eukaryotic cells. The required evidentiary showing, pointing to some motivation, suggestion or teaching in the art of the desirability of making the specific modification, in particular, a non-yeast eukaryotic cell composition having a diverse population of about 10 or more variant nucleic acids wherein each variant nucleic acid is located within each cell at an identical site in the genome, that was made by the inventors is lacking from the assertions in the Office Action. While the Office provides an "advantageous effect of obtaining a product from the library with higher affinities," the federal case law requires that the evidentiary showing be clear and particular and does not allow for broad conclusory statements about

the teachings of the cited references. Accordingly, the cited art to Stemmer and Biard-Piechczyk et al. fail to teach, suggest or provide a motivation for one skilled in the art to carry out the claimed invention with a reasonable expectation of success.

In light of the Remarks herein, Applicant contends that the claimed invention is unobvious over the cited art. Accordingly, Applicant respectfully requests withdrawal of the rejection under § 103 over Stemmer in view of Biard-Piechczyk et al.

Conclusion

Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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